

What is claimed is:

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1. A biologically active TGF- $\beta$  family member fusion protein competent to refold under suitable refolding conditions, comprising:
  - a TGF- $\beta$  family protein C-terminal seven cysteine domain, comprising a finger 1 subdomain, a finger 2 subdomain, and a heel subdomain; and
  - a heterologous leader sequence domain operatively linked to said C-terminal domain.
2. The fusion protein of claim 1 wherein said leader sequence is selected from the group consisting of a tissue-targeting domain, a molecular-targeting domain, a metal-binding domain, a protein-binding domain, a ceramic-binding domain, a hydroxyapatite-binding domain, and a collagen-binding domain.
3. The fusion protein of claim 2 wherein said tissue-targeting domain binds to a bone matrix protein.
4. The fusion protein of claim 2 wherein said tissue-targeting domain binds to a cell surface molecule.
5. The fusion protein of claim 4 wherein said cell surface molecule is on an osteoprogenitor cell or a chondrocyte.
6. A latent TGF- $\beta$  family member fusion protein competent to refold under suitable

refolding conditions, comprising:

a TGF- $\beta$  family protein C-terminal seven cysteine domain, comprising a finger 1 subdomain, a finger 2 subdomain, and a heel subdomain; and  
a cleavable leader sequence operably linked to said C-terminal domain wherein said leader sequence inhibits the biological activity associated with said C-terminal domain, and wherein said C-terminal domain becomes active upon cleavage of a part or all of said leader sequence.

7. The fusion protein of claim 6 wherein a tissue-targeting domain is embedded within said cleavable leader sequence, whereby cleavage of the leader sequence will not cleave said tissue-targeting domain from said C-terminal domain.

8. The fusion protein of claim 1 or 6 wherein said leader sequence is separated from said C-terminal domain by at least seven residues.

9. The fusion protein of claim 1 wherein said leader sequence is derived from another TGF- $\beta$  family protein.

10. A biologically active TGF- $\beta$  family member protein mutant competent to refold under suitable refolding conditions, comprising:

a TGF- $\beta$  family member protein C-terminal seven cysteine domain, comprising a finger 1 subdomain, a finger 2 subdomain, and a heel subdomain; and  
a leader sequence domain operatively linked to said C-terminal domain, whereby a part or all of said leader sequence is truncated.

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11. The protein mutant of claim 10 wherein said truncation is carried out by protease cleavage.

12. The protein mutant of claim 11 wherein said protease is trypsin.

13. The protein mutant of claim 10 wherein said truncation is carried out by chemical cleavage.

14. The protein mutant of claim 15 wherein said chemical cleavage is acid cleavage.

15. The protein mutant of claim 10 wherein at least one basic residue of said leader sequence is removed.

16. The protein mutant of claim 10 wherein said protein mutant consists essentially of amino acid sequence SEQ ID NO. 69.

17. A biologically active heterodimer of TGF- $\beta$  family member proteins, comprising:  
a first subunit being a TGF- $\beta$  family member fusion protein; and  
a second subunit selected from the group consisting of a TGF- $\beta$  family member fusion protein different from that of the first subunit and a wild type TGF- $\beta$  family protein.

18. The heterodimer of claim 16, wherein said wild type TGF- $\beta$  family protein is

selected from the group consisting of TGF- $\beta$ 1, TGF- $\beta$ -2, TGF- $\beta$ 3, TGF- $\beta$ 4, TGF- $\beta$ 5, dpp, Vg-1, Vgr-1, 60A, BMP-2A, BMP-3, BMP-4, BMP-5, BMP-6, Dorsalin, OP-1, OP-2, OP-3, GDF-1, GDF-3, GDF-9, Inhibin  $\alpha$ , Inhibin  $\beta$ A and Inhibin  $\beta$ B.

19. A method of purifying a heterodimer of TGF- $\beta$  family proteins, said method comprising:

- (a) providing a first TGF- $\beta$  family protein subunit;
- (b) providing a second TGF- $\beta$  family protein subunit different from said first subunit;
- (c) mixing said first subunit and said second subunit under suitable refolding conditions to generate a mixture comprising
  - (i) a first homodimer comprising two of said first TGF- $\beta$  family protein subunits;
  - (ii) a second homodimer comprising two of said second TGF- $\beta$  family protein subunits; and
  - (iii) a heterodimer comprising one of said first TGF- $\beta$  family subunits and one of said second TGF- $\beta$  family subunits;
- wherein said heterodimer is separable from said first homodimer and said second homodimer; and
- (d) separating said heterodimer from said first homodimer and said second homodimer.

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